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Summary

This paper studies the interaction between two dynamic domains, (1) an evolutionary biological system ('the environment') whose behaviour determines the availability of a resource stock, and (2) an industry where access to the resource stock is determined by the outcome of a patent race. The specific setting of the model is that of managing microbial resistance to antibiotics. Here, resistance develops in response to the use of antibiotics above a threshold level. We show that the optimal policy from society's point of view is to generate through R&D a diversified portfolio of antibiotics that maintains a steady-state of resistance. In practice, however, the management of the resistance stock is left to an industry operating under a system of intellectual property rights (IPR). There, firms are involved in a sequence of patent races to supply the antibiotic with the best cost-effectiveness ratio. The paper studies the structure of the patent race within the industry against the background of pathogen evolution. We show that a multi-firm industry operating under an IPR-based incentive mechanism is unlikely to generate the socially optimal number of antibiotics because IPR systems (1) create incentives for sequential rather than simultaneous innovation; (2) generate incentives that decline with the number of previous (shelved) discoveries; and (3) generate incentives that respond perversely to increases in biological system velocity. These results highlight the importance of well-designed dynamic incentives for managing resource stock dynamics.

Keywords: Resource management, intellectual property rights, evolution, resistance, antibiotics

JEL: I0, Q0

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1. Introduction

This paper studies the interaction between two dynamic domains. The first is an evolutionary biological system where 'evolutionary' refers to the system's adaptive response to changes in its environment. In this paper, adaptive change is welfare-relevant to the extent that it determines the availability of an essential resource in the economy. We introduce novel tools from mathematical evolutionary biology to describe the behaviour of the biological system over time. The second dynamic domain involved is an industry in which access to the essential resource is determined by the outcome of a patent race. To analyse this part, we draw on the theory of industrial organisation where the structure of such races has previously been studied.

What interests us in this paper is the nature and welfare implications of the dynamics that the interaction between these two domains generates. To characterise their nature, we first derive the optimal management solution for the evolutionary biological system and then contrast this solution with the outcome generated by the industry dynamics. We are able to identify a number of novel welfare implications associated with patent races when such races interact with another dynamic domain. Specifically, we show that patents represent an ineffective response to the management requirements demanded by an evolutionary system.

Various reasons for inefficiencies in a patent system are well documented in the economic literature. First of all, patents invariably represent a second-best response to the competing objectives of rent creation (through stimulating new innovations) and rent diffusion (by non-exclusion of potential users) (Klemperer 1990). Secondly, the 'winner-takes-all' pay-off structure inherent in the race for monopolistic rents may lead to wasteful duplication of R&D efforts and excess investment into R&D (Dasgupta and Stiglitz 1981). Thirdly, more than the socially optimal amount of resources may be spent on enforcing patent rights (Maskus 2000). And fourthly, transaction costs required to enable patents to be exchanged on markets may be excessive (Spence 1975). These inefficiencies point towards the importance of correctly designing the breadth (scope), height (minimum improvement), and length (duration of protection) of the intellectual property right. The inefficiencies identified in this paper are more fundamental: We find that rewarding firms for gaining access to the resource stock through time-delimited monopoly rights (such as patents) creates an undesirable pattern of R&D investment. This implies that the very idea underpinning a patent, namely the award of a time-limited monopoly, is incompatible with the optimal management of the type of system we describe here. Patents fail to resolve the underlying management problem. From this we conclude that alternative reward regimes need to be explored in these settings.

What is the practical relevance of the problem this paper studies? The origins of the paper lie in previous work we have conducted on managing evolutionary predator-prey relationships (Goeschl and Swanson 2002a, Goeschl 1998) and evolutionary systems (Goeschl and Swanson 2002b). The specific policy setting that motivates this paper is the problem of antimicrobial resistance. There, the essential resource is the effectiveness of antimicrobials (or antibiotics). These products allow the control of pathogen populations (bacteria, fungi, etc) that cause significant welfare effects through their impact on public health. The excessive use of such products, however, triggers adaptive changes in the pathogen population by creating selection pressure within the population, leading to an increase in pathogens resistant to the antibiotic. By so reducing the effectiveness of antibiotics, the evolution towards resistance impacts on the availability of the essential resource in the public health sector. These dynamics constitute the evolutionary biology system requiring management.

A number of papers study the optimal management of this biological system from the social planner perspective when one or, at most, two antibiotics are available (Laxminarayan and Brown 2001, Wilen and Msangi 2002, Brown and Layton 1996, Cornes et al. 1995). What sets this paper apart from this literature is the explicit consideration of the industry dynamics that augment the stock of effectiveness by creating new antibiotics. These dynamics originate in R&D investment decisions and intersect with the biological system on account of the impact that pathogen evolution has on the time profile of effectiveness of the products so developed.

The R&D activities are carried out by firms under a specific regime of rewards that society has put in place to enable firms to capture parts of the social rents created by the development of new antibiotics. The specific regime is one of intellectual property rights (IPR), most commonly patent rights. Their function is to grant innovating firms time-delimited monopolistic rents in order to reward R&D. The availability of effectiveness over time will therefore be jointly determined by the evolution toward resistance by pathogens and the R&D activity within industry carried out in expectation of patent rents. This interaction does not produce results that accord with the socially optimal R&D policy.

The paper proceeds as follows: Section 2 develops the background on which the dynamics of the evolutionary biological system rest. Section 3 characterises the social planner's management of these dynamics. This constitutes the benchmark case against which the outcome under IPRs will be assessed. Section 4 develops the response of private agents in a market setting to the development of resistance. The main institutional feature of this setting is an IPR system that governs the rewards to innovation. We compare the various aspects of the interaction between the IPR system and the evolutionary dynamics of resistance with the socially optimal solution and conclude in section 5.

2. The evolutionary biological system

There are a number of mathematical models available that describe the evolutionary behaviour of biological systems and that lend themselves to use by economists (Goeschl 2000). The most common form are models based on variants of the fundamental replicator equation. This equation originates in the Hardy-Weinberg law of genetic evolution. These models have since become popular in evolutionary game theory (Hofbauer and Sigmund 1988, Weibull 1992, Fudenberg and Levine 1998). A second basic model is that of "matching allele" games between hosts and pathogens. We have used this model previously to model the optimal composition of a gene bank to supply genetic material for crops that are hosts to pathogens (Goeschl and Swanson 1998). In this paper, we use an alternative formalisation of intertemporal dynamics based on the so-called *'lag load' model of evolution* (Maynard Smith 1976).[1] This model yields qualitatively equivalent results to genetic selection models based on the Hardy-Weinberg law with the benefit of greater applicability across various evolutionary settings.

2.1. The lag load model

The concept of the lag load is related to the concept of ecological fitness. In the ecological literature, there have been attempts to give a numerical measure of the fitness position of an organism. To do so in absolute terms is not possible, but it is feasible to define the current fitness relative to a concrete reference point, the local adaptive peak. This definition device is called the "evolutionary lag" or "lag load" (Stenseth and Maynard Smith 1984, Maynard Smith 1976) and is denoted as

$$L = \frac{\hat{F} - \overline{F}}{\hat{F}} \qquad (1)$$

where $\overline{F}$ is the mean of the fitness of the population under consideration and $\hat{F}$ is the fitness of the "fittest possible genotype incorporating all mutations favourable in the *contemporary* environment, whether they are already present in the population or have yet to occur" (Stenseth and Maynard Smith 1984). The lag load L is therefore a measure of the evolutionary potential of a population. Higher values of L indicate higher chances for a fitness-enhancing trait to reach fixation, i.e. to establish itself in the population. The origins of this trait can lie in mutation, recombination or latency and thus allows for both pre-adaptive and post-adaptive change.[2]

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[1] For an explicit discussion of the lag load model and its use in evolutionary models of this type, see Goeschl (2000).

[2] Replicator equation models are usually limited to pre-adaptive change, i.e. variants that existed prior to evolutionary pressure being exerted.

It is important to recognise that the lag load model does not explicitly consider population dynamics which are important drivers of dynamics in replicator equation models. In other words, with a view to the greater time scale of the lag load model, it is assumed that populations are always operating at their equilibrium levels. This greatly simplifies the analysis, but necessarily neglects epidemiological aspects.

2.2. The evolution of antibiotic resistance

How does the lag load concept relate to the evolution of resistance to some antibiotic *i*?. Maynard Smith (1976) defines the rate of evolution (for example towards resistance) as a function of the lag load, *L*, induced by some selection pressure (such as antibiotic *i*). The lag load with respect to *i* is a function of the average fitness relative to the local adaptive peak given the presence of *i* such that the increase in the share of pathogens v_i in the population under consideration that is resistant to antibiotic *i* is (Maynard Smith 1976):

$$\dot{v}_i = f(L_i) = f\left(\frac{\hat{F}_i - \overline{F}_i}{\hat{F}_i}\right) \qquad (2)$$

where $f(0)=0$ and $f(.)$ is a monotonically increasing function. an be summarised in the evolution function (Maynard Smith 1976)

$$\dot{v}_i = \frac{\partial v_i}{\partial L_i} \cdot \dot{L}_i \qquad (3)$$

What remains to do is to link the evolution of resistance in equation (3) to a notion of biological fitness. We suppress the index *i* for this part. A common way to operationalise the concept of biological fitness in biology is to assume that fitness of the individual pathogen is $(1 + r)$ with *r* denoting the individual's contribution to growth (Roughgarden 1979). Two considerations matter in establishing the contribution to growth of an individual pathogen. The first is the cost of carrying a resistance gene. This cost manifests itself in a lower growth rate of the resistant pathogen since resources are diverted from growth to defense. It is therefore commonly assumed that the growth rate of the resistant pathogen r_R is smaller than the growth rate of the susceptible pathogen where no antibiotic is used. For convenience we define that $r_R = r - a$ with *r* denoting the 'baseline' growth rate of the susceptible pathogen in the absence of an antibiotic and the constant $a>0$ denoting the cost of resistance measured in terms of growth. Conversely, where the antibiotic is used, the fitness of susceptible pathogens is reduced such

that in this case $r_S = r - d$ with the constant $d>a>0$ denoting the death rate on account of the antibiotic.

The second consideration is spatial mobility of pathogens between treated and non-treated locations within an environment. This is important for the dynamics because the fitness of the *susceptible* pathogens will differ considerably between treated and non-treated settings. We denote the rate of out-migration of pathogens from a location with the parameter *m.*

The cost of resistance *a* and rate of spatial mobility *m* interact in a simple, but intuitively rich, way in the behaviour of the evolutionary system under selection pressure. Assume the antibiotic is used on a share $0<f<1$ of locations. The average lag load of pathogens under selection pressure consists of the stationary share *(1-m)f* of (resistant and susceptible) pathogens under treatment plus the share *m(1-f)* of immigrating pathogens not under selection pressure(remember that all populations are in equilibrium). Formally, the average fitness under treatment is

$$\begin{aligned}\overline{F} &= (1-m)f\left[v(1+r-a)+(1-v)(1+r-d)\right]+m(1-f)\left[v(1+r-a)+(1-v)(1+r)\right] \\ &= 1+r+(1-v)a-(1-m)(1-v)df\end{aligned} \quad (4)$$

Expression (4) can be related to the lag load through equation (1) which gives the relative distance of the average population fitness from the local adaptive peak.[3] Applying (1) to (4) results in

$$Lag = \frac{\hat{F}-\overline{F}}{\hat{F}} = \frac{-(1-v)a+(1-m)(1-v)df}{1+r} \quad (5)$$

When the functional form of adaptive speed $f(.)$ in equation (2) is quadratic, the change of resistance per time unit effected by pathogens due to exposure to treatment is

$$\dot{v} = -\partial v / \partial Lag \cdot Lag^2 e \quad (6)$$

with *e* denoting the selection pressure elasticity of fitness. Combining (5) and (6), the share of resistant pathogens is

$$\dot{v} = -\frac{(1+r)e}{a-(1-m)df}\cdot\left[\frac{-(1-v)a+(1-m)(1-v)df}{1+r}\right]^2$$

which can be simplified into expression (7) stating the evolution of resistance with respect to antibiotic *i* as a function of migration and cost of resistance (assumed to be not antibiotic specific)**:**

[3] Since $a>0$ and $d>0$, maximum fitness is $\hat{F} = (1+r)$.

$$\dot{v}_i = \left[(1-m)df_i - a\right](1-v)^2 \frac{e}{1+r} \qquad (7)$$

There are several statements that can be made about expression (7). The first concerns the net evolutionary pressure contained in the first parentheses. This contains the engine that drives evolution towards resistance. As a benchmark case, for migration m at zero and no cost to resistance ($a=0$), the pathogen population will evolve to resistance at rate $d \cdot f_i$, i.e. proportional to the death rate d inflicted on susceptible pathogen and the scale of treatment f. If resistance has a cost a, then there exists the possibility of a steady state in resistance at positive levels f_i of use of antibiotic i such that $(1-m)df = a$. This also highlights the importance of the migration rate as a higher migration rate allows higher levels of antibiotics use at the same level of evolutionary pressure on the treated pathogen population. This mirrors Comins' (1977) conclusion that if resistance genes are sufficiently recessive (i.e. there is a cost to resistance) and if pathogens are spatially mobile, then the pathogen population under treatment can absorb a certain amount of exposure to treatment without triggering evolution towards resistance. Similarly to Comins, note that in the interest of tractability the lag load -based model understates the evolutionary pressure from very high levels f_i of treatment with antibiotic i because expression (7) does not explicitly take into account the dynamics of the pathogen population *as a whole*. Note also that for (7) to hold, $f_i>0$, i.e. treatment levels have to be positive.[4]

The second component in expression (7) is the adaptive speed that translates evolutionary pressure into evolution. It defines the marginal impact from the application of treatment-based selection pressure as a function of the present level of resistance. This captures the standard evolutionary dynamics from the introduction of a single pathogen with increased fitness. Specifically, the less frequent resistance is within the population, then the greater is the 'fitness' of a resistant pathogen relative to the average pathogen in the population and the greater the impact of the introduced unit of resistance (i.e. the single resistant pathogen). The marginal impact of selection on the frequency of resistance is therefore greater at lower levels of resistance.[5] Evolution stops once full resistance has been reached ($dv_i/dt=0$ for $v_i=1$). Finally, the third component of the dynamic system is the parameter e, which represents the elasticity of relative fitness (second parentheses) with respect to net selection pressure (first parentheses). Due to other environmental factors mitigating resistance development, $e<1$ will typically hold.

[4] Otherwise, different dynamics apply. This highlights the asymmetry between the evolutionary dynamics in the presence or absence of treatment. Resistance does therefore not neatly fit the features of either a non-renewable or renewable resource.

[5] This feature is also well known from models based on the Hardy-Weinberg law.

Based on expression (7), we are able to describe the responsiveness of the system to different treatment programs, in a way that is both general and tractable. The spatial setting for the model depends on the pathogen and the treatment program under consideration. For some pathogens the model describes the interaction of the host population within a metropolitan area, and outpatient treatment programs. For other pathogens the model describes the interaction of the host population on a single hospital ward, and the treatment program corresponds to the antibiotic prescription policies applied on that ward. We wish to use the model as a general framework for considering the appropriate strategies society should use for addressing the problem of antibiotic resistance as described by this dynamic system, and the problems with using market-based incentive mechanisms for addressing the same system.

This concludes our discussion of the evolutionary framework underlying our approach. We now turn to the social planner's problem of minimising the costs of infections within the context of the dynamic system we have described here. The solution to this problem defines the benchmark against which the non-cooperative solution established under a patent race can be contrasted.

3. The optimal management of the evolutionary biological system

We assume that the objective of the social planner is to minimise the costs of evolving infectious diseases to society over an infinite time horizon. Two main instruments are available to deal with the disease problem: Treatment through the use of antibiotics and development of new antibiotics. These two instruments are related through the evolutionary mechanism developed in the previous section: Higher level of use of an antibiotic allows the treatment of more patients, but depletes its effectiveness. The development of new antibiotics may therefore become desirable, at a cost of R&D to society. There is therefore a direct link between the demand for treatments (higher use) and the supply of treatments (through more R&D). A similar type of linkage has previously been studied in the literature on exhaustible resources and backstop technologies (Dasgupta and Heal 1974, Dasgupta and Stiglitz 1981, Tsur and Zemel 2002). Our characterisation of the solution to the social planner problem is related to this literature, but there are also important differences that set the problem of antibiotics resistance apart from the exhaustible resource setting.

At the outset, we make a number of assumptions that define a tractable policy problem based on the biological literature.

ASSUMPTION 1: *There is an equilibrium per-period flow of patients H = 1 carrying pathogens.*[6]

ASSUMPTION 2: *Each patient carries only one type of pathogens which (a) cannot be identified a priori, (b) is therefore resistant to antibiotic i with probability v_i or susceptible with probability (1-v_i),*[7] *and (c) cannot be treated with more than one antibiotic per period.*

ASSUMPTION 3*: Disease that is not or not successfully treated causes a homogeneous and constant fixed cost D per patient.*

These assumptions define an epidemiological system comprising a very large susceptible human host population and some common pool of pathogens that humans encounter on a periodic basis.[8] This interaction between hosts and pathogens creates a constant flow of patients that seek treatment, but where it is not known whether they carry a resistant or susceptible 'bug'. Whether treatment is carried out or not (or is not successful), patients do not return for treatment. Based on assumptions 1 through 3, the social planner has to consider three main cost components in the optimisation problem. The first is simply the sum of treatment costs $\Sigma f_i c_i$, which are the costs of procuring amount f_i of antibiotic i at cost c_i. (2) a cost of disease D per patient, which is incurred either through non-treatment or - with probability v_i - unsuccessful treatment, and (3) cost of R&D R incurred in the search for new antibiotics.

Before stating the social planner's problem, we need to define the R&D process that supplies new antibiotics to the treatment sector. These new antibiotics represent new stocks of effectiveness that can be exhausted through treatment.

ASSUMPTION 4: *Antibiotics are generated by a continuous-time Poisson process with probability* $\beta\Lambda(R(t))$ *where* β *is the common Poisson parameter of per-period likelihood, and* $\Lambda(R(t))$ *is the R&D output as a function of R&D investment* $R(t)$ *at time* t*. In line with convention,* $\Lambda(0)=0$, $\Lambda'(R(t))>0$, $\Lambda''(R(t))<0$.

ASSUMPTION 5: *Each innovation has the same initial effectiveness v_0.*

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[6] We therefore ignore epidemiological dynamics within the human population.

[7] It would be more general to assume that the incidence of unsuccessful treatment is an increasing function of the proportion of resistant pathogens, but without the additional assumption of linearity. We adopt linearity as a simplifying assumption, but recognise that the investigation of threshold and other effects are important subjects for further research.

[8] In other words, like in Comins' (1977) in his analytical results, we assume perfect density dependence in the pathogen population.

ASSUMPTION 6: *The unit cost of producing a new antibiotic is revealed after the innovation has been made and is drawn from a uniform probability distribution over the cost interval* $\left[\underline{c},\bar{c}\right]$.[9]

Assumptions 4 through 6 describe a standard stochastic R&D process that at a cost of R&D *R* generates innovations (here: antibiotics) of which the cost-effectiveness characteristic (the ration of v_0 to c_i) is not exactly known prior to discovery.

3.1. The social planner's problem

Given the modelling assumptions 1 through 3, the *value of the social planner's treatment programme* is

$$\int_{t=0}^{\infty} e^{-pt}\left[D\left(-1+\sum_{i=1}^{n(t)} f_i(t)(1-v_i(t))\right)-\sum_{i=1}^{n(t)} c_i f_i(t)\right]dt \qquad (8)$$

with *D* denoting the disease-related damage in the absence of (successful) treatment, f_i the share of patients treated with one antibiotic *i* out of *n(t)* available antibiotics at time *t*, $(1-v_i)$ the probability of an unsuccessful treatment with antibiotic *i* (where *v* is the share of pathogens resistant to antibiotic *i* within the pool), and c_i denoting the cost of antibiotic *i*.

On the treatment side, the dynamic and static constraints on maximising (8) are the evolution of resistance (equation (7)) and constraint on the total amount of applications in any period not to exceed the number of patients such that for each antibiotic *i*

$$0 \le f_i \le 1 \quad \text{and} \quad \sum_{i=1}^{n(t)} f_i \le 1 \qquad (9)$$

On the R&D side, the social planner faces an innovation process of the Poisson type with intensity $bL(R)$ and $n=\{n(t):t=0\}$ taking discrete values $\{0,1,2,3,\ldots\}$ such that

$$\Pr\left(n(t+h)=n+m \middle| n(t)=n\right)=\begin{cases} b\Lambda(R)h+o(h) & \text{if } m=1 \\ o(h) & \text{if } m>1 \\ 1-b\Lambda(R)+o(h) & \text{if } m=0 \end{cases} \qquad (10)$$

[9] This is similar to models of mining where the grade and extraction cost of ore is not know prior to the discovery of the mine (Slade 2001).

Expression (10) describes a standard Poisson process that generates one innovation (and typically not more than one) in the time interval *(t,t+h)* with probability *bL(R)*. The *social planner's problem* is therefore

$$\max_{\{f_i,R\}} \int_{t=0}^{\infty} e^{-pt}\left[D\left(-1+\sum_{i=1}^{n(t)} f_i(t)(1-v_i(t)) \right) - \sum_{i=1}^{n(t)} c_i f_i(t) - R(t) \right] dt \qquad (11)$$

$$\text{subject to } v(0) = v_0, \lim_{T\to\infty} v(T) \text{ free, (7), (9) and (10).}$$

Expression (11) states the social planner has to minimise the cost of infectious diseases to society through simultaneously choosing optimal level of use f_i for each one of the *n(t)* treatments available at time *t* and the optimal level of investment *R* into the development of additional treatments.

In order to solve problem (11), note that equation (8) consists of *n(t)* separable choice problems that are linear in the control variable $f_i(t)$. These *n(t)* separable problems are interrelated through the static constraint (9) and constitute the treatment problem. Overlaid onto the treatment problem is question of how to generate the optimal time path for *n(t)* through the R&D process. This is a discrete step-wise process that is - again - linked to the treatment problem primarily through the constraint (9) as we will see. Instead of solving problem (11) in a direct assault, an equivalent but more convenient approach is to analyse the treatment and R&D problem sequentially, by holding *n(t)* constant initially and then studying the optimal path for *n(t)* over time. This approach has the advantage of enabling us to characterise the optimal solution to the problem in an intuitively appealing way by making full use of the analytics of the current-value Hamiltonian.

3.2. The optimal treatment programme

In this section we provide a solution to the treatment problem (8) under the assumption of *n(t)* being held constant. We concentrate here on the solutions and their prescriptive content while the explicit derivations and proofs can be found in the appendix.

The treatment problem (8) for *n* antibiotics subject to constraints (7) and (9) can be solved by using a mixed-constraints Hamiltonian of the form

$$H(n) = -D + \sum_{i=1}^{n(t)} \left\{ \left[D(1-v_i(t)) - c_i - k(t) \right] f_i(t) + m_i(t)\left[(1-m) df_i(t) - a \right](1-v_i(t))^2 \frac{e}{1+r} \right\} + k(t) \qquad (12)$$

which is linear in the control variable $f_i(t)$. This structure gives rise to a switching function such that the optimal choice of f_i is governed by the following conditions:

$$f_i = \begin{cases} 0 \text{ if } m_i < \mathrm{M}_i \\ f_i^*(t) \text{ if } m_i = \mathrm{M}_i \\ 1 \text{ if } m_i > \mathrm{M}_i \end{cases} \qquad (13)$$

$$\text{with } \mathrm{M}_i = \frac{c_i - D(1-v_i) + k}{(1-m)d(1-v_i)^2 \dfrac{e}{(1+r)}}$$

M_i defines the *shadow cost of resistance to antibiotic i* along the singular solution. Expression (13) states the feedback decision rule to be followed by the social planner. The first part states that the antibiotic *i* ought not to be used if the expected disease-induced damage avoided through treatment, $D(1-v_i)$, is less than the cost of treatment itself plus the shadow cost of exploiting the stock of the antibiotic's effectiveness plus the opportunity cost of using an alternative antibiotic. Conversely, the third part states that if the expected damage avoided is greater than the treatment cost plus shadow cost, then all patients should be treated with the antibiotic. Along the singular solution $v_i^s(t)$, treatment will be held at a level $f_i^*(t)$. Solving for the singular solution $v_i^s(t)$, we arrive at a use policy for each antibiotic *i* that has up to four path segments which is defined in proposition 1.

PROPOSITION 1: For $n(t)$ constant and $v_0 > v_i^*$ for all antibiotics *i*, the optimal use path of antibiotic *i* consists of up to four segments: (1) An initial period of non-use during which $f_i=0$ for $(n-1)$ antibiotics, (2) either a most-rapid approach path (MRAP) from v_0 to the non-stationary singular solution $v_i^s(t)$ during which $f_i=1$ and antibiotic *i* is the only product used and/or (3) a non-stationary singular solution (NSS) path involving other antibiotics than *i* during which $f_i^* > a/(1-m)d$ and that converges to the unique and stationary singular solution v_i^*, and (4) a stationary singular solution (SSS) v_i^* during which $f_i^* = a/(1-m)d$ for all antibiotics used at time *t*.

Assuming that antibiotics are heterogeneous in cost of application c_i and start from an identical resistance level v_0, the above proposition implies that the optimal treatment programme given a set of *n* antibiotics will involve the sequential introduction of antibiotics. Each will be introduced in order of cost c_i. The most cost-effective antibiotic will be introduced first on a MRAP where all patients will be treated ($f_i=1$) until its total economic cost (instantaneous cost, shadow cost of resistance and the shadow cost associated with constraint (9)) reaches a point in time t_s with an associated level of resistance $v_i^s(t_s)$ at which the second-best antibiotic becomes cost-effective. Then the second antibiotic together with the first are used together on a NSS path to treat all patients until their total economic costs render the next antibiotic feasible, etc. This process of phasing -in continues in this way until all antibiotics reach their cost-specific SSS v_i^*. Proposition 2 characterises the social planner's welfare position after convergence to the steady state defined by the SSS.

PROPOSITION 2: If $v_i=v_i^*$ for all $i \in n(t)$, $dv_i/dt = 0$ for all i and $\Sigma f_i = \min[n(t)/N, 1]$ with $N=(1-m)d/a$.

Proposition 2 implies that as long as $n(t)<N$, it is optimal not to treat a share $(1-n(t)/N)$ of patients once the steady state of the SSS has been reached. Treatment of each case is optimal only during the transition to the steady state along a MRAP or the NSS.

Propositions 1 and 2 together define the 'technological endpoint' to the problem of resistance. This endpoint is characterised by a diversified treatment portfolio of size N at which the evolutionary pressure d exerted by each antibiotic on the non-migratory pathogen population $(1-m)$ equals the cost of resistance a. Expanding the set of available antibiotics to N has two welfare-relevant implications for the social planner: The first is at $n(t)=N$, it is optimal to treat every patient. This means that at the 'technological endpoint' there is no instantaneous welfare loss imposed by long-run considerations of resistance development. The second is that since $dv_i/dt=0$ for all i in N, there is no resistance cost to steady-state use of antibiotics which allows full treatment to continue. An expansion to a portfolio of size N at the SSS is therefore associated with both instantaneous and dynamic welfare gains. These gains are sensitive, however, to time periods of transitional dynamics to the SSS involving MRAPs or NSSs where no untreated cases arise. There is therefore a non-trivial dynamic link between the treatment policy defined in propositions 1 and 2 and the expansion of the portfolio from some current level $n(t)<N$ to N requiring resources R to be spent on the R&D process described in (10). We study the linkage between treatment and R&D and characterise the optimal closed-loop policy rule for R&D expenditure $R(t)$ in the following section.

3.3. The optimal R&D programme

The optimal R&D programme consists of two distinct phases involving different optimal policies. The juncture dividing the two phases is the 'technological endpoint' to the resistance problem that is reached by expanding the portfolio to N antibiotics while following the optimal treatment programme set out in proposition 1. After reaching N, R&D policy reverts to solving the standard problem of cost reduction in production of treatments. In the present set-up, this involves R&D activity that is directed to discover antibiotics with a production cost $c_{n+1} <\max [c_1, c_2,\ldots, c_n]$ in the cost interval defined by assumption 6. Prior to reaching N, R&D is motivated not only by cost reduction, but also by welfare gains generated by the reduction in disease costs.

In solving for the optimal R&D policy rule, we tackle the discrete stepwise nature of growth in $n(t)$ by using the expected value of the current-value Hamiltonian of the $(n+1)$th antibiotics as the

R&D investment criterion at time t . This investment criterion is optimal in the sense that the current value Hamiltonian equals the constant-equivalent flow of well being to which the 'project' (here a new antibiotic) gives rise (Weitzman 1976). The value of the current-value Hamiltonian will be determined by the current treatment policy that generates a shadow value for the *(n+1)*th antibiotic, thus establishing the formal link between the demand side and the supply side of treatments.

To derive the optimal policy rule, recall that the Hamiltonian function (12) describing the treatment programme given n antibiotics can be broken up into n linearly separable Hamiltonians of the format

$$H_i = [D(1-v_i(t)) - c_i - k(t)]f_i(t) + m_i(t)[(1-m)df_i(t) - a](1-v_i(t))^2 \frac{e}{1+r} \qquad (14)$$

such that

$$H(n) = -D + \sum_{i=1}^{n(t)} H_i + k(t) \qquad (15)$$

The R&D process (10) is such that through investment of *R(t)* at time *t*, the social planner holding a set *n(t)* has a probability of $bL(R(t))$ that the set of antibiotics will expand to *n(t)+1*. It follows from (15) and (10) that the R&D problem at time *t* is to choose *R(t)* such that the expected current constant equivalent pay-off from R&D net of R&D costs is maximised. Lemma 1 establishes the optimal choice for *R(t):*

LEMMA *1:* Given (15) and (10), and with H_{n+1} denoting the Hamiltonian of format (14) associated with the *(n+1)*th antibiotic, the optimal R&D intensity *R(t)* at time *t* is such that

$$b\Lambda'(R(t))H_{n+1} = 1. \qquad (16)$$

PROOF*:* The Hamiltonian given *n+1* antibiotics, *H(n+1)*, is linearly separable into *n+1* Hamiltonians along the lines of (15). For any given time *t*, H_{n+1} is therefore the difference *H(n+1,t)* - *H(n,t)*. The solution to the maximisation problem

$$\max_{R(t)} b\Lambda(R(t))[H(n+1,t) - H(n,t)] - R(t) \qquad (17)$$

is therefore to set *R(t)* such that $bL(R(t))\, H_{n+1} - R(t) = 0$, which is the root of equation (16).

We can further specify H_{n+1} based on the expected cost of the new antibiotic $E[c_{n+1}]$ from assumption (6) and initial resistance v_0 from assumption (5).

$$H_{n+1} = \left[D(1-v_0) - E\left[c_{n+1}\right] - k(t)\right] f_i(t) + m_i(t)\left[(1-m)df_i(t) - a\right](1-v_0)^2 \frac{e}{1+r}$$

(18)

In the first set of parentheses in expression (18), we can identify the variable driving the R&D process, namely the shadow cost *k(t)* associated with constraint (9). This shadow cost can be interpreted as the total cost-effectiveness threshold implied by average antibiotic in use at time *t* along the optimal treatment programme. This has an intuitive interpretation to Lemma 1 in that the use of an antibiotic with either low cost or high effectiveness along the MRAP or NSS requires marginal productivity of the R&D process to increase. Since $L''(R)<0$ (assumption 4), this implies a reduction of R&D investment during that time. Any policy on the MRAP or NSS involves declining effectiveness v_i of any antibiotic *i* in use since $f_i > a/(1-m)d$ (Proposition 1), which implies a decreasing shadow cost ($dk/dt<0$) for $k>0$ and *n* constant. On the other hand, this also implies that incentives for R&D are the greatest when the treatment policy has settled down to the SSS while $n(t)<N$ since the SSS is associated with a shadow cost $k=0$ prior to reaching the 'technological endpoint' of diversification. Proposition 3 characterises the socially optimal R&D policy rule that results from the interaction of the optimal treatment programme contained in proposition 1 and the R&D optimum stated in Lemma 1.

PROPOSITION 3: Denote the level of R&D after reaching *N* with $R_c(k)>0$ for $n(t)=N$ and with $R_A(t)>0$ the non-negative root of equation (16) when $k(t)=0$. Then if $R_c(k)$ exists, $R_A(t)$ exists and $R(t) = R_c(k)$ for $n<N$ along MRAP and NSS and $R(t)=R_A(t)<R_c(k)$ along the SSS. Otherwise, $R(t)=0$ along the MRAP and NSS and $R(t)=R_A(t)$ along the SSS.

Proposition 3 states that if R&D is worthwhile for cost-saving objectives alone, some R&D will be carried out during the MRAP and NSS even before reaching the technological endpoint in order to replace existing antibiotics with cheaper substitutes (as will be after reaching *N*). Additional R&D will be carried out during the SSS with the objective of extending the antibiotics portfolio. Otherwise, no R&D will be carried out during these treatment phases and after reaching *N* and as long as equation (16) has a non-negative root, R&D will be carried out during the SSS as long as $n(t)<N$. This means that if R&D is worthwhile on cost grounds alone, then it is optimal to devote additional resources to expanding the portfolio to reach *N*. Proposition 4 characterises the nature of these additional resource more.

PROPOSITION 4: If $n(t) < N$, R&D incentives in the SSS are invariant to the current number of antibiotics $n(t)$.

PROOF: For $\kappa=0$, H_{n+1} does not depend on $n(t)$ since

$$H_{n+1}(t) = D\left[(1-v_0) - \frac{1}{r+V}\right] - E(c_{n+1})\left[1 - \frac{[(1-m)d-a]}{(1-m)d(1-v_0)(r+V)}\right]$$

$$\text{with } V = [(1-m)d-a]\frac{e}{1+r}(1-v_0)$$

Proposition 4 states that evaluated at a time when the treatment programme is in the SSS, the optimal level of R&D expenditures does not depend on the existing number of antibiotics. The reason is that the constant-equivalent flow of value generated by the R&D project is the net disease costs saved by the treatment of a constant share *a/(1-m)d* of patients in perpetuity. This means that the incentives for R&D **based on reduction in disease cost** will not decline with the number of antibiotics already discovered. There are therefore constant welfare returns to R&D activity from the vantage point of long-run disease costs to society. Naturally, the (additional) incentives for cost reducing R&D do decrease with *n*. An obvious corollary of proposition 4 is therefore that if R&D is carried out for cost-reduction purposes at some point, then society must reach the 'technological endpoint' of a portfolio of *N* antibiotics in finite time since *R(t)>0* for all *t* where *n(t)<N*.

The last aspect to be studied with respect to the optimal R&D policy is how responsive it is to changes in the behaviour of the evolutionary system. We examine here the change in incentives for R&D generated by a higher elasticity of relative fitness with respect to net selection. This elasticity is captured in parameter *e* and is a broad indicator for the speed of evolutionary response: Higher elasticity, i.e. a higher value of *e*, implies a more rapid development of resistance. To assess the incentives for R&D with respect to *e*, we evaluate the partial derivative of the current-value Hamiltonian with respect to an increase in *e*.

PROPOSITION 5: For $n(t)<N$ and $D > E[c_{n+1}][(1-m)d-a]$, the optimal level of investment at time, *R(t)*, increases with increases in the elasticity of relative fitness, *e*.

PROOF: We restrict the analysis to the SSS without loss of generality. Since

$$\frac{\partial H_{n+1}}{\partial e} = \frac{V}{\frac{de}{1+r}[r+V]}[D - E(c_{n+1})((1-m)d-a)]$$

which is greater than zero for $D > E[c_{n+1}]$ $[(1-m)d-a]$, the root of equation (16), namely the marginal productivity of R&D, implying under assumption (4) that R&D spending $R_A(t)$ has to increase in response to a higher level of *e*. Note that $[(1-m)d-a]<1$, such that $D>E[c_{n+1}]$ is sufficient for proposition 5 to hold.

The content of proposition 5 is intuitively appealing: If the cost to disease D is greater than the average expected cost of treatment $E[c_{n+1}]$, then more rapid development of resistance increases the shadow cost of resistance. This raises the social marginal product of R&D, making it optimal to direct more investment to the R&D process. The social incentives for R&D increase therefore if society fasces more rapidly evolving pathogens.

We conclude from propositions 1 through 5 that if disease costs matter and if R&D in production cost reduction is rational, then social planner will always pursue the construction of a diversified portfolio of treatments in order to solve the problem of resistance up to N antibiotics. Along the SSS, R&D into new antibiotics generates constant returns to scale that are independent of the current size of the portfolio. Once the technological endpoint is reached through this R&D process, the entire portfolio will be used simultaneously at a level of use that keeps level of antibiotics effectiveness constant. Further R&D will be carried out at this stage in order to generate less expensive substitutes for the existing set of products, but will not affect the diversified nature of the treatment policy. A greater adaptive speed of pathogens results in higher R&D investment. The following section will contrast this social optimal management approach to resistance management with the approach generated by an uncoordinated market system operating under an IPR system to reward innovation.

4. Industry dynamics

This section analyses the R&D behaviour generated by instituting a reward system based on IPR when interacting with an evolutionary system of the type described in section 2. The nature of the reward system is that it rewards firms for accessing the essential resource of effectiveness through the development of a new antibiotic with initial effectiveness level $(1-v_0)$. Specifically, we want to assess whether IPR regimes provide the sorts of incentive mechanisms that will generate R&D investments directed towards the social objective developed in section 3. Accordingly, this section develops equivalent propositions regarding the treatment policy (Proposition 1), the R&D policy (Proposition 3, the change in R&D incentives as the portfolio expands (Proposition 4), and the change in R&D as a result of increasing speed of adaptive change (Proposition 5) in a noncooperative setting under IPR.

The noncooperative setting comprises two sets of players: The first set of players are the users of antibiotics. These users constitute the demand side of the management problem. The other set of players comprises antibiotics producers individually characterised by the two parameters of their product at time t, the current effectiveness $(1-v_i(t))$, the unit cost of treatment, c_i and the price p_i.

These variables are part of the common information set of all market participants. This second set of players constitute the supply side of the management problem. The reason for a deviation of noncoordinated management of the evolutionary system approach from the socially optimal policy characterised in section 3 can therefore be caused by characteristics of the demand or the supply side.

Similar to the structure of section 3, we first analyse the demand for treatment and then progress to the incentives for R&D.

4.1. Demand for treatment

We first look at the demand side for treatments with assumptions 1-3 holding.

ASSUMPTION 7: *Users choose the most cost effective treatment possible at time* t.[10]

From assumption 7 follows Lemma 2.

LEMMA 2: For every point in time t and v_i/p_i ? v_j/p_j for all $i,j \in n(t)$, there is one firm that supplies D.

This lemma results directly from the assumptions set forth above. Since antibiotics are perfect substitutes in treatment, assumption 7 implies a decision rule for users to choose treatment $j[1,2,\ldots,n]$ at every point in time such that

$$j = \arg\max\left[\frac{(1-v_1)}{p_1}, \frac{(1-v_2)}{p_2}, \ldots, \frac{(1-v_n)}{p_n}\right] \qquad (19)$$

where p_i denotes the price of strategy i. Unless there are two strategies with identical benefit-price ratios, this decision rule yields a uniform choice of treatment for all users.

Lemma 2 highlights the first fundamental problem in using an uncoordinated market to manage antimicrobial resistance. For products that are essentially substitutes, the market rewards the producer who can provide the good at least cost. This necessarily leads to a homogeneity in market output that contrasts with the socially optimal diversification objective for the long run set out in Proposition 1.

To a large extent, much of the focus on the problem of antibiotic resistance has been on this consumer-driven problem of uniformity in treatments. Proposed solutions to the demand side problem then involve limitations on the use of a single treatment (e.g. by the use of permits), and hence the

[10] This assumption merely implies that the socially optimal solution to the antibiotic resistance problem is not being pursued via treatment decisions being made at the individual level, either by consumers, their doctors or their hospitals. It is likely that the incentives generated by medical liability laws will render this assumption noncontroversial in most jurisdictions.

creation of market niches for other treatments such that assumption 7 (and therefore Lemma 2) cannot hold (Laxminarayan and Weitzman 2001). This situation could arise in the context of antimicrobial resistance if – as suggested by some policy-makers - hospitals would start diversifying their treatment portfolios. However, can IPR-based R&D incentives generate the antibiotics to fill these niches created through such regulation of the demand side? The following section shows that there is a fundamental result in the theory of industrial organisation that applies to this question.

4.2. Incentives for R&D under market-sharing

Let us assume that in order to solve the demand side problem through diversification a shared-market solution is commanded in some fashion. This means that a market-based mechanism is retained but the market for antibiotic treatments (for a given infection) is required to be shared between a number of different firms and the various antibiotic treatments they produce. Successful innovators enter the market by discovering the *(n+1)*th antibiotic and are restricted by virtue of an inelastic demand function to share the market in with one or more incumbents. This market-sharing has two effects: A quantity effect that results from confining the innovator to a fraction of the total market and a possible price effect that limits pricing power. These two effects result in proposition 6:

PROPOSITION 6: Incentives for R&D decline with the number of incumbents in a shared-market solution.

We omit a proof of proposition 6 since it is not more than a special case of the so-called 'efficiency effect' (Gilbert and Newbery 1982, Tirole 1988) under conditions of inelastic unit demand. The efficiency effect states that under identical production technology, monopolistic profits strictly exceed those of two duopolists, while those of two duopolists strictly exceed those of three oligopolists etc until any remaining market power is completed dissipated across the firms in the industry. Although production technology will ex post (i.e. after the innovation has been made) differ between firms as they will draw different cost schedules from the cost distribution interval $\left[\underline{c},\bar{c}\right]$, ex ante firms will expect an identical average cost $E[c_{n+1}]$ that will determine their incentive to invest.

The efficiency effect states generally (and proposition 6 specifically) that a shared market in antibiotics cannot generate the same level of profits per participant as a wholly-owned one. There are two distinct reasons. First, and most obviously, the market (and its available rents) are divided by the increasing number of participants. Secondly, and more importantly, the increased level of market participation reduces the extent to which market sharing accords with monopoly rent division. As the

number of market participants increases, the possibility that the shared monopoly outcome will persist declines, even if there are enforcement mechanisms available.

In order to create incentives for entry through R&D, therefore, the efficiency effect has to be counteracted by a reward for innovation. This reward is the creation of temporary monopolies through an IPR. It gives rise to the so-called 'replacement effect' (Arrow 1962, Tirole 1988). By its nature, the replacement effect fails to maintain incentives for R&D if the innovating firm is forced to share the market with one or more incumbents. The IPR system therefore creates a sequence of monopolies in order to create incentives for R&D investment and by so doing incentives for sequential rather than simultaneous innovation.

The relevance this conclusion for an evaluation of the interaction between IPR systems and antibiotics is evident in comparison with the propositions 1 and 3. The social planner will aim at both a diversified treatment strategy (except in the transitional phase) together with a R&D policy that creates an expanding portfolio. A combination of regulation in the demand side and an IPR regime on the other hand is not capable of both diversifying treatment and simultaneously rewarding the creation of such a portfolio by competing innovators. The reason is that in essence, an IPR regime operates by means of conferring sequential monopolies, and market-splitting is incompatible with maintaining levels of R&D investment under such a regime. We now proceed to focus on the problems inherent in the R&D decisions given an IPR system to derive the equivalent counterparts to propositions 4 and 5.

4.3. The supply of new antibiotics over time

Proposition 6 states that IPR systems will generate incentives for sequential innovation rather than simultaneous. This means that it certainly will not be targeting the socially optimal solution concept outlined in section 3; however, it does not prove by itself that sequential innovation is incapable of generating a socially optimal portfolio, albeit eventually. The ability of an IPR system to generate a portfolio over time will depend on how the incentives to invest in R&D respond to respond to previous innovations.

The antibiotics industry R&D problem has many parallels to the patent races explored in much of the modern R&D literature (Dasgupta and Stiglitz 1981, Reinganum 1985), but differs in that the "winner takes all" (WTA) pay-off structure is slightly altered. To see why, it is sufficient to realise that each firm, after successfully innovating can find itself in one of two positions. Either it has produced the strategy that will supersede the one currently in use or it has produced some strategy with a higher cost. In the standard WTA situation, the net present value of the innovation is zero in the second case.

In the present model, there is a potentially positive present value to shelved innovations. The reason is the following: The pay-off from a patent on a strategy in use is eroding over time because of the loss of treatment effectiveness as pathogens evolve. As this happens, previous innovations become competitive. The chance of a previous innovation superseding a depreciated strategy thus creates an incentive for innovation. Clearly, this incentive decreases with the number of antibiotics already shelved at the point of innovation and on the number of innovations that have been shelved since that point which is in itself a function of the aggregate R&D expenditures.

The novelty in this setting is therefore that the loss of effectiveness of an antibiotic in monopolistic use has two effects on the incentives for R&D. The first is to raise the expected pay-off from innovation since even initially unsuccessful R&D output has the potential to create rents when competitors' products loose effectiveness. The second is to lower the expected pay-off from innovation since in the presence of shelved innovations a new innovation is less likely to replace the incumbent, offers a shorter effective period of rent extraction if replacement occurs, and depresses the value of any shelved innovations owned by the innovating firm itself. The first effect will increase the incentive for R&D, the second will reduce the incentive.

The compound effect of shelving has an ambiguous incentive effect on total R&D expenditure on the industry. However, the effect is clear with respect to whether a patent race with shelving can generate a diversified portfolio of treatments over time. Building on the R&D process defined in assumptions 4 through 6 and expression (10) and denoting with $b\,l(x_i)$ firm *i*'s per-period probability of a discovery given R&D investment x_i, let the monopolistic rents (if any) from the $(n+1)$th innovation be denoted by V_{n+1}, the probability of replacing the incumbent by $s_{n+1}(t)$ and the expected value of shelving the $(n+1)$th innovation by F_{n+1}. Adapting the standard R&D balancing condition from (Reinganum 1985) for the case of shelving, the optimal R&D level for firm *i* then fulfils the condition:

$$b\,l'(x_i)s_{n+1}V_{n+1} + b\,l'(x_i)(1-s_{n+1})\Phi'_{n+1}(x_i) + b\,l'(x_i)\sum_n \Phi'(x_i)_n - 1 = 0 \qquad (20)$$

Expression (20) states that the optimal R&D expenditures of firm *i* are at the point where the marginal cost of R&D (*1*) equals the marginal gain in the expected value of replacing the incumbent strategy plus the marginal gain in the expected value of generating a new strategy that can be shelved plus the expected marginal loss in the value of previously shelved innovations.[11] Taking into account the R&D expenditure of all other firms, equation (20) determines the optimal level of R&D for firm *i*, x_i^*, as a function of decision of all other firms, leading to proposition 7.

PROPOSITION 7: Firm *i*'s optimal R&D investment at time *t*, $x_i^*(t)$ decreases with the number of shelved innovations *n(t)*.

This proposition has three aspects: The first is the impact of shelved innovations on the volume of rents after replacing the incumbent through an innovation, the second their impact on the probability of superseding the incumbent monopolist, and the third the substitution effect and 'own' replacement effect generated by new innovations that are shelved. These distinct effects reduce incentives for R&D in a situation where companies have developed a number of antibiotic strategies and that can be deduced from equation (20).

4.3.1. Monopolistic rents after replacing the incumbent

The value of the monopolistic position after a successful innovation (one that replaces the incumbent) is diminished by the contestable market effect and the monopoly duration effect. From equation (20), the value to firm *i* of superseding the current strategy in use *n* (implying *n-1* innovations shelved) with a new innovation *n+1* is

$$V_{n+1} = \int_{t=0}^{\infty} \exp\left\{\left[-r - b\,s_{n+1}(t)\sum_{h\neq i} l(x_h)\right]t\right\}\Pi_{n+1}(t)dt \qquad (21)$$

where r is the discount rate, b is the probability of a success in the current period, s is the probability of a competitor's innovation superseding the current strategy and h is the number of firms engaging in R&D and x their R&D expenditure. The expected value is therefore the stream of profits, P_{n+1}, generated by being the producer with the highest benefit-cost ratio on the market, discounted by the opportunity cost of capital r and the risk that another innovation replaces the firm as supplier. Profits are

$$\Pi_{n+1}(t) = \max\left[0;\left(c'\frac{1-v_{n+1}(t)}{1-v'} - c_{n+1}\right)\right] \qquad (22)$$

where the second best strategy in terms of price-benefit ratio available at that moment are denoted with *v'* and *c'*. Under a uniform distribution of production costs, the probability of being replaced, $s_{n+1}(t)$, can be written explicitly as

$$s_{n+1}(t) = c_{n+1}\frac{1-v_0}{1-v_{n+1}(t)} \qquad (23)$$

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[11] The last component will necessarily be negative as any innovation by *i* has a positive probability of outperforming a shelved innovation from the past.

The monopolistic rent V_{n+1} depends on the effectiveness of the current strategy, the unit cost of the current strategy, the unit cost of the innovation and the unit cost of other shelved strategies in a non-trivial and dynamic way. For firms with identical cost of innovation and distribution of unit costs of production, we can then re-write V_{n+1} having solved for $v_i(t)$ and P_{n+1} and denoting with x^* the Nash equilibrium strategy of each firm:

$$V_{n+1} = \int_{t=0}^{T} \exp\left\{\left[-r - b\left(c_{n+1}\frac{t(1-v_0)+a}{a}\right)(h-1)l(x^*)\right]t\right\}\Pi_{n+1}(t)dt \qquad (24)$$

$$\text{with } T = \frac{1}{(1-a)e}\left(\frac{c'}{c_{n+1}(1-v')} - \frac{1}{(1-v_0)}\right) \qquad (25)$$

Equation (24) can now be used to demonstrate the contestable market effect and the monopoly duration effect: First, note that the expected marginal cost of the second best strategy, *c'*, declines with the number of shelved strategies.[12] The profit expression, P_{t+1}, is that from equation (22). This states that because the second-best product can contest the market as soon as the monopolist charges more than the marginal costs of the second-best competitor, monopolistic rent extraction is limited. This limitation constrains further as the number of shelved innovations and - accordingly - *c'* increase. The monopoly duration effect relies on the same mechanism: With *c'* decreasing as the number of strategies increases, the duration of monopoly *T* decreases as well, this limiting the effective time of rent extraction. A related observation about equation (24) is that v_{n+1} will be rising over time as resistance to antibiotic *n+1* increases. This means that superseding an incumbent strategy *(v',c')* that had lost little of its effectiveness incurs low profits. This is because the scope for rent extraction in (24) is low and the period of rent extraction in (25) short. In other words, profit incentives strongly favour a slow turn-over of strategies and discourage innovation when a successful product is around.[13]

4.3.2. The probability of replacing the incumbent

[12] This can be easily demonstrated using elementary probability theory. Take some random point on the cost continuum and any stochastic process generating independently and identically distributed random numbers. The probability of at least one of the random numbers being below the chosen point increases with the number generated.

[13] At least in theory, the probability of using a shelved product is a possible reason for R&D investment in antibiotics exceeding that in other pharmaceuticals in which effectiveness of competitors' products does not decline. This value is clearly positive and hence a source of R&D incentives. The extent to which this outweighs the disincentives that endogenised resistance creates is an empirical question.

The contestable market effect and the duration effect were derived by reference to the expected monopolistic profit stream of a successful innovation. However, an increase in the number of shelved innovations also impacts on the probability that an innovation is sufficiently inexpensive to produce that it actually allows the innovator to replace the incumbent. This impact gives rise to the 'threshold effect' captured in expression s_{n+1} in equation (20). As in the previous case, a high number of existing strategies reduces the probability of replacing the monopolist for an innovator by decreasing the probability of having the least-cost strategy. The probability of developing a strategy that has to be shelved, $(1- s_{n+1})$, increases by the same amount. The value of shelving the $(n+1)$th innovation, F_{n+1}, must be strictly lower than the value of replacing an incumbent monopolist, V_{n+1}, however. This difference, i.e. $V_{n+1} - F_{n+1}$, gives rise to the threshold effect as the marginal cost of an innovation has to lie below an increasingly lower expected critical threshold in order to replace the monopolist as the number of shelved innovations increases.

4.3.3. The substitution effect and 'own' replacement effect

The value of the shelved strategy, F_{n+1}, is not only strictly lower than V_{n+1}, it is also itself sensitive to the number of shelved innovations $n(t)$. This is because any shelved strategy is competing for least-cost not only against the current existing strategies, but also all the innovations developed in the meantime that can substitute for it. This is the source of the substitution effect. The more innovations are already shelved, the less the value of shelving an innovation and hence the reward for R&D.

Finally in equation (20), there is the unique version of Arrow's (1962) replacement effect in that there is a cost to innovation if the firm already has strategies shelved. The value of these strategies, $\Sigma_n F'(x_i)_n$, will decrease in the event of an innovation as it will delay the expected time at which a shelved strategy can be marketed. This implies that own R&D reduces the expected value of own strategy. This is a weaker form of the “Arrow effect” or “replacement effect” as the expected value of the strategy is lower than the monopolistic profit.

We have therefore established five distinct effects that give rise to a negative link between the number of shelved strategies in the sector and the incentives for private R&D. Shelving either limits the rents generated by a monopolistic market position (through the contestable market and the duration effect) or it negatively affects the probability of superseding the incumbent (threshold effect) or the

value of (previously) shelved innovations (substitution and 'own' replacement effect). Proposition 7 therefore represents the dynamic version of proposition 6. The latter states that a monopolistic market structure is required to maintain incentives for R&D. This explains why IPRs represent a reward structure geared towards sequential innovation rather than simultaneous innovation. Proposition 7 states that if industry generated simultaneous innovations, the IPR system would ensure that further R&D would be reduced until a sufficient share of the accumulated stock of innovations had been sequentially put to use. This contrasts with the socially optimal R&D policy expressed in proposition 4 that requires continuous innovation until a portfolio of size *N* has been reached.

4.4. Increasing resistance and R&D

Propositions 6 and 7 highlight the static and dynamic factors that are likely to prevent an IPR regime from generating incentives that target the socially optimal level of diversification. As the IPR system constrains firms to a pattern of innovation over time, the "technological endpoint" cannot be reached under the limitations of such an institutional setting. However, the propositions do not prove that the aggregate level of funds expended on R&D by private firms are sub-optimal under the institutional constraint of sequential innovation. This is clearly an area of further research although previous work on the private sector response to evolutionary depreciation of patent values suggests that a system based on private IPR incentives leads to under-investment in R&D by private firms (Goeschl and Swanson 2002).

A clear divergence between socially optimal choice and the outcome generated by private firms can be ascertained on the basis of equations (24) and (25). This divergence concerns the private sector response to an increased speed of resistance development and therefore the correspondence to proposition 5 assessing the socially optimal response to an accelerated evolutionary system. Proposition 5 states that pathogens that develop resistance more rapidly than others clearly should attract more R&D. The response of the private sector to reduce R&D investment is the basis of proposition 8.

PROPOSITION 8*: Private firms react to an increasing speed of resistance development with a reduction in R&D expenditures.*

PROOF**:** Pathogens with a faster rate of evolution towards resistance are characterised by a higher elasticity of selection with respect to selection pressure, *e*. This faster rate of evolution has an impact on monopolistic profits through the expected duration of the monopoly. Taking the derivative of equation (25) with respect to the elasticity of selection shows that the duration of monopoly and speed of resistance development are inversely related.

$$\frac{\partial T}{\partial e} = -\frac{1}{(1-a)e^2}\left(\frac{c'}{c_{n+1}(1-v')} - \frac{1}{(1-v_0)}\right) \qquad (26)$$

This implies that the total rent accruing to an innovator will be lower if the pathogens treated with the new antibiotic are more responsive to selection pressure or if environmental conditions change towards a more rapid development of resistance. The resultant reduction in rents depresses the incentives for innovation such that the rate of new product development can be expected to be lower.[14] The private sector response will therefore be diametrically opposite to the response that a social planner would pursue.

5. Conclusion

The optimal solution to managing the evolutionary biological system described in part 2 lies in the development of a portfolio of treatments broad enough to allow every patient to be treated (proposition 3) while following a diversified treatment programme while approaching this broad portfolio except during transitional phases (proposition 1). This enables in the long run the management of the system without incurring a resistance cost at the aggregate level (proposition 4). The more rapid the biological system evolves, the more resources should optimally be allocated to R&D.

Why is it the case that there is little or no evidence of the pursuit of the first best management of resistance such as in the case of antibiotics? We have argued that the decentralised structure of the industry and the delimited nature of the incentive system provide no incentive to pursue the vast majority of the social benefits available from the use of this strategy. The success of IPR systems as system of rewards for innovation relies on the creation of temporary monopolies, in other words on sequential innovation. We have shown that such a system cannot support the creation of a broad portfolio of competing products, even if the demand for such a diversification existed or was required through intervention (proposition 6). We have also argued that even if a broad portfolio arose, it would effectively prevent further resources from being expended on R&D of antibiotics (proposition 7).

The misalignment between social optimum and private solution is of a fundamental nature. The institutional answer to the problem of rent appropriation from innovation not only prevents an approximation of a diversified array of treatments. It also presumes a positive link between social benefits and private rents, if not in size then at least in direction. This presumption need not hold. The

obsolescence of innovation through evolutionary dynamics is a case in point. It leads to a reduction in R&D spending on innovations when an increase would be socially desirable (proposition 8). The conclusion has to be then that there is little or no incentive within this system to consider the potentially socially beneficial implications of the discovery and use of greater numbers of antibiotics across populations and across time. These horizons are lost.

[14] Clearly, the faster rate of depreciation of effectiveness creates incentives for other innovators to capture rents more quickly. It can be shown, however, that this 'business stealing' effect (Aghion and Howitt 1992) is outweighed by the impact on expected rents. See Goeschl and Swanson (1999) for a full discussion of the countervailing effects at work.

Appendix:

Here we derive propositions 1 and 2.

The current-value Hamiltonian for the treatment problem is

$$H(n) = -D + \sum_{i=1}^{n(t)} \left\{ \left[D(1-v_i(t)) - c_i - k(t) \right] f_i(t) + m_i(t) \left[(1-m) d f_i(t) - a \right] (1-v_i(t))^2 \frac{e}{1+r} \right\} + k(t)$$

with the Kuhn-Tucker condition

$$k\left(\sum_{i=1}^{n(t)} f_i - 1 \right) = 0 \qquad \text{(A1)}$$

and the switching function (13) from the first order condition on $H(n)$. The switching function (13) supports path segments (1) for $m_i(t)<M$ (non-use) and (2) for $m_i(t)>M$ (most rapid approach path) in proposition 1. Path segments (3) and (4) require the time path for the co-state variable m_i along the singular solution:

$$\dot{m}_i = \frac{\partial m_i}{\partial v_i} \dot{v}_i + \frac{\partial m_i}{\partial k_i} \dot{k}_i = \frac{(1-m) d f_i - a}{(1-m) d} \left(\frac{2c_i}{1-v_i} - D \right) + \frac{1}{(1-m) d \frac{e}{1+r} (1-v_i)^2} \dot{k}_i \qquad \text{(A2)}$$

and the time path of the co-state variable implied by the first order conditions on (12):

$$\dot{m}_i = r m_i + D f_i + 2 m_i \left[(1-m) d f_i - a \right] \frac{e}{1+r} (1-v_i) \qquad \text{(A3).}$$

(A1), (A2), and (A3) define the singular solution to (12) while (13) defines the optimal control off the singular solution path. The singular solution of v_i^s, is the non-negative root of the quadratic function

$$r \left[c_i - D(1-v_i) \right] + \frac{ae}{1+r} (1-v_i)^2 D = \dot{k} \qquad \text{(A3).}$$

From (A3) follows that for $dk/dt=0$, there is a stationary (time-invariant) singular solution (SSS) v_i^*. From $v_i^*(t)=v_i^*$, the equation of motion (7) and constraint (A1) follows that $f_i^*(v_i^*(t)) = a/(1-m)d$ in the SSS. This conclusion supports segment (4) of the optimal path in proposition 1. If $k>0$ (from (9) and (12)) and $f_i^*(t)>a/(1-m)d$ due to (13) then $dk/dt<0$ (from switching function (13)) which implies that there is a non-stationary singular solution (NSS) $v_i^s<v_i^*$ that converges to v_i^* over finite time. This conclusion supports segment (3) in proposition 1.

If $n(t)<N=(1-m)d/a$, the equation of motion (7) and Kuhn-Tucker condition (A1) imply the existence of a SSS with $k=0$. Since in the SSS, $f_i^*(v_i^*(t)) = a/(1-m)d$ for all $n(t)$, a share of $(1-n(t)a/(1-m)d)=1-n(t)/N$ of cases will not be treated in the singular solution. We thus prove proposition 2.

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